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Development and external validation of a mpMRI- and ISUP-based add-on prediction tool to identify prostate cancer candidates for pelvic lymph node dissection

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Brief descriptive runninghead: State-of-the-art add-on nomogram to predict N1 prostate cancer

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Abstract

Purpose: To expand the current prediction tools for lymph node invasion (LNI) in prostate cancer (PCa) patients with today's state-of-the-art available tumor information, including multiparametric MRI (mpMRI)-based tumor (T) staging and detailed biopsy information.

Materials and methods: PCa patients with registered ISUP-based biopsy information and mpMRI information, who underwent a radical prostatectomy with extended pelvic LN dissection, were selected. A LNI prediction tool was developed in 420 patients and externally validated in 187 patients. A concordance index was estimated to quantify the discriminative performance of the model.

Results: In the development cohort, a median of 21 LN was removed per patient. Seventy one patients (16.9%) were diagnosed with LNI. Statistically significant predictors of LNI were the iPSA value, mpMRI-based T-stage, maximum tumor-length-in-one-core (mm) and ISUP grade group corresponding to the maximum tumor-involvement-in-one-core. The predictive accuracy of this LNI prediction tool was 79.7% after 5-fold internal cross validation and 72.5% at external validation.

Conclusion: We report a contemporary, externally validated prediction tool for the presence of LNI in PCa patients. This prediction tool answers to the paradigm shift from systematic biopsies towards targeted biopsies by incorporating additional core-specific biopsy information instead of the percentage of positive cores. This new tool will also overcome stage migration, which is a potential risk when mpMRI information is used in digital rectal exam based nomograms.

Introduction

Prostate cancer (PCa) is the most common non-skin malignancy and an important cause of cancer-related mortality in men ¹. Up to 15% of PCa patients undergoing radical prostatectomy with extended pelvic lymph node dissection (ePLND) harbour lymph node invasion (pN1) at the time of surgery ². Since lymph node invasion (LNI) was found to be an independent risk factor for prostate specific antigen (PSA) recurrence and cancer-related death in patients with PCa, it is important to identify patients at increased risk for LNI ³. Until now, performing an ePLND has proven to be the most accurate nodal staging procedure and remains therefore the gold standard ⁴.

Unfortunately, performing an ePLND could potentially induce postoperative complications and morbidity depending on the extension of the PLND ⁵. The superior diagnostic accuracy of an ePLND

1 should therefore be weighed against its higher risk of morbidity. However, this staging technique
2 remains justified in well-defined PCa patient groups since particular groups of patients with pN1
3 disease benefit from adjuvant androgen deprivation therapy (ADT) with or without radiotherapy^{6,7}.

4 Several nomograms were developed to distinguish patients where ePLND could be omitted safely
5 from those who should be considered for ePLND⁸⁻¹⁰. These nomograms incorporate the
6 preoperative PSA value, primary and secondary biopsy Gleason grade, the percentage of tumor
7 positive cores and clinical tumor (cT)-stage to predict the risk of LNI. Both the EAU and NCCN
8 guidelines recommend the use of these models to select patients for ePLND^{11,12}. These prediction
9 tools must be updated periodically since major shifts in both the presentation grade and stage of PCa
10 can influence the accuracy of the developed nomograms¹³. According to the NCCN guidelines, a cut-
11 off that allows the avoidance of roughly 50% of PLNDs prior at the cost of missing 12% of patients
12 with LNI is considered acceptable¹².

13 With the advent of functional imaging procedures for local and distant staging, nomograms might
14 need to be changed as these new imaging tools might have predictive power themselves. Concerning
15 local staging, a multiparametric MRI (mpMRI) is increasingly performed to increase cT-stage accuracy
16 and to guide prostate biopsy. Unfortunately, the existing prediction models are lacking information
17 obtained by preoperative mpMRI. All models incorporate the cT-stage achieved only by digital rectal
18 examination (DRE). However, DRE results could be subject to inter-observer variability and up to 25%
19 of the PCa tumors are located in the transition zone which cannot be reached by DRE¹⁴⁻¹⁶.

20 Furthermore, there is a paradigm shift from systematic biopsies towards MRI-targeted biopsies^{17,18}.
21 In order to accommodate to this evolution, we investigated whether the percentage of positive cores
22 used in the current nomograms could be replaced by detailed biopsy information instead, as a
23 surrogate for tumor volume.

24 **Materials and methods**

25 *Patient population*

26 This retrospective study was approved by the institutional ethical review boards of UZ Leuven (UZL)
27 (S61215) and AZ Groeninge Hospital Kortrijk (AZG) (AZGS2018101). Patient charts were reviewed for
28 1559 patients who were treated with an open (n=943) or robot-assisted (n=616) radical
29 prostatectomy (RP) between January 2008 and December 2017 at UZL. Patients with complete data
30 who underwent biopsy specimen review by one of three dedicated uropathologists (BW, EL and TG),
31 imaging evaluation by one of three urologists experienced in prostate imaging (RO, LDW and
32 EV), and RP combined with a PLND (≥ 10 lymph nodes (LNs) removed) were selected (n=491)¹⁹. In

our center, all high risk and high-intermediate risk PCa patients underwent standardly an ePLND. For low-intermediate risk patients the decision to perform a PLND was based on the existing nomograms, although suboptimal for target biopsied patients, using a cut-off of 5%^{8,10}. Patients receiving previous local or systemic therapy (n=24) and patients who were staged cN1/M1 (n=47) by CT, MRI and bone scintigraphy before surgery were excluded from our analysis.

Clinical and pathological evaluation

Patient characteristics were extracted from the medical files and included age, initial PSA (iPSA) value, image-based tumor (iT)-stage by mpMRI evaluation, tumor multifocality and zonal tumor location. mpMRI was performed on a 1.5 T magnet (Aera; Siemens Medical Systems, Erlangen, Germany) (UZL) or 3.0 T magnet (Discovery MR750w; GE Healthcare, Milwaukee, WI, USA) (AZG). Axial, coronal and sagittal T2-weighted MRI, axial T1-weighted MRI and axial diffusion weighted MRI (DWI), covering the prostate gland, seminal vesicles and the pelvis up to the aortic bifurcation, were acquired. Local staging was performed based on features described in the literature²⁰⁻²³.

Systematic (29.5%) (median: 10 cores; IQR: 10-12 cores), targeted (24.3%) (median: 4 cores; IQR: 3-7 cores) and combined (46.2%) (median: 12 cores; IQR: 12-14 cores) prostate biopsies were processed in accordance with the ISUP guidelines. Pathological evaluation was performed according to the ISUP grading system^{24,25}. The ISUP grade group on biopsy for each positive core, the percentage of tumor involvement and exact tumor length in each core and the percentage of positive biopsy cores were recorded.

The endpoint of our trial was prediction of LNI, defined as presence of positive LN at final histopathological evaluation. Since it is clear that staging accuracy increases by extending the LN dissection template, we decided to use a cut-off of at least 10 removed LN as surrogate of a well performed ePLND^{26,27}.

Statistical analysis and model building

Descriptive statistics include absolute and relative frequencies for categorical variables, and the median and interquartile range for quantitative variables. Patient groups were compared using the Mann-Whitney U test for continuous variables and the χ^2 -test for categorical variables. First, the choice of the most predictive biopsy parameters was based on an initial exploratory analysis. Four combinations of biopsy parameters were compared to each other and the best fitting combination was selected for final model building. Model 1 and 2 are 'length-of-involvement-in-one-core'-based models. Model 1 is based on the highest ISUP grade biopsied and the maximum tumor-involvement-in-one-core of this highest ISUP grade biopsied, whereas model 2 is based on the overall maximum

tumor- length-involvement-in-one-core combined with its corresponding ISUP grade group. Models 3 and 4 are 'percentage-of-positive-cores'-based models. Model 3 is based on the overall percentage of positive cores and the percentage of cores with highest grade disease and the percentage of cores with lower grade PCa. Model 4 is based on the percentage of positive biopsy cores of the most common biopsied ISUP grade, combined with this most common ISUP grade. Selection was based on the Akaike's information criterion (AIC) in multivariable logistic regression. The best combination of biopsy parameters to predict LNI is the combination for which the AIC is the lowest.

Subsequently, we developed a multivariable model predicting LNI. The choice of included biopsy parameters was based on the selected model from the initial exploratory analysis. Furthermore, the iPSA value and the earlier mentioned mpMRI parameters were investigated as potential predictors for model building. A logistic regression modelling with LNI as binary outcome variable was performed. A backward selection procedure was applied for model building, with a 5% significance level to identify and select variables to stay in the model. A concordance index (C-index), which corresponds to the area under the receiver operating characteristic curve (AUC), was estimated to quantify the discriminative performance of the model. A C-index value of 1.0 indicates perfect discrimination, while 0.5 is equivalent to a toss of a coin. A 5-fold cross validation was performed to correct for over-optimism of the C-index. Decision curve analysis was performed to explore the clinical effects of our prediction tool. All statistical analyses were performed using SAS software (version 9.4 of the SAS System for Windows).

External validation

After the development of the prediction model, an external validation study was performed to explore whether predictions done by the model are valid in a different population. Patient charts were reviewed for 266 patients who were treated with RP and ePLND between March 2015 and October 2018 at AZG. Patients with complete registered data regarding biopsy, imaging and final pathology evaluation including ePLND (≥ 10 LN) were selected (n=187) for external validation.

Results

Patient characteristics

Pre- and postoperative characteristics of the 420 patients of the development cohort are shown in Table 1. The mean age at surgery was 65 years (IQR: 60-70). At mpMRI, 180 (42.9%) patients had iT1 or iT2 disease, 224 (53.3%) iT3 and 16 (3.8%) iT4 PCa. The iPSA value, iT-stage by mpMRI evaluation, zonal tumor location on mpMRI and multiple biopsy parameters differed significantly among patients

with and without LNI ($p \leq 0.05$). Of the 420 included patients, 71 (16.9%) patients were diagnosed with LNI at final pathology.

Comparison and selection of biopsy information

In a first step, four different multivariable models were fitted to predict LNI, accounting for different biopsy characteristics, to select the most informative combination of biopsy parameters. The C-indices and AICs were calculated and are shown in Table 2. Model 2, based on the overall maximum tumor-length-involvement-in-one-core combined with its corresponding ISUP grade group, achieved the highest C-index (0.78) and lowest AIC (327.3) and was selected as the best predicting biopsy-based model. An additional non-interacting effect was found between the maximum tumor-length-in-one-core and the corresponding ISUP grade group.

Multivariable prediction model for LNI

Based on the initial exploratory analysis, biopsy information as mentioned in model 2 was used for further analysis. At multivariable analysis, iPSA value, mpMRI-based iT-stage, maximum tumor-length-in-one-core (mm) and the ISUP grade group corresponding to the maximum tumor-involvement-in-one-core were independent predictors of LNI (Table 3; $p < 0.05$). These four parameters were fitted in a multivariable model predicting for LNI. During the backward selection procedure, tumor multifocality on mpMRI and zonal tumor location on mpMRI were not identified as discriminating factors for LNI. Our multivariable mpMRI-based model to predict LNI achieved a C-index of 0.81 (95% CI: 0.76 – 0.87). A 5-fold cross-validation analysis was performed as initial evaluation of the accuracy of the model in predicting LNI. A C-index of 0.80 was obtained. The final multivariable model is summarised in Table 3 and can be launched by scanning a QR-code (Figure 1).

External validation

Patient characteristics of the 187 patients of the external validation group are shown in Table 4. Of these, 26 (13.9%) patients were ultimately diagnosed with LNI. When applying the developed prediction tool to the external validation cohort, a C-index of 0.73 was reached. A calibration plot showing the actual versus predicted probability of LNI was drawn for each decile (Figure 2) and shows a tendency towards overprediction of the actual risk.

LNI thresholds

Prediction tool-derived probability cut-offs from 1% to 20% were tested (Table 5). The numbers of avoidable ePLNDs and potentially missed LNI are reported. Decision curve analysis revealed a greater

net benefit of using the developed prediction tool for the threshold probabilities compared to treating all or no men (Figure 3).

Discussion

Nodal staging is of utmost importance to identify PCa patients at higher risk of disease recurrence and cancer-related death in order to optimize and intensify their treatment^{6,7}. The gold standard for accurate nodal staging remains the performance of an ePLND⁴. Given the potential postoperative complications and morbidity of ePLND⁵, patients should be well-selected before performing this procedure. The EAU and NCCN guidelines recommend the use of the Briganti and MSKCC nomograms to select patients for ePLND^{8,10}. Although these nomograms are associated with good performance characteristics, they are not fully adapted to the state-of-the-art staging procedures. Neither nomogram takes into account mpMRI information or is adapted to the paradigm shift from systematic biopsies towards targeted biopsies, whether or not in combination with systematic biopsies^{17,28}. In particular for low-intermediate risk PCa patients, our prediction tool could be used as an add-on tool to the existing DRE-based and systematic biopsy-based nomograms to (further) select patients for ePLND.

Our results demonstrate that detailed biopsy characteristics such as the overall maximum tumor-length-involvement-in-one-core combined with its corresponding ISUP grade group represent independent predictors of LNI. Furthermore, the developed prediction tool is tailored to the ISUP grade grouping as proposed by the EAU guidelines¹¹.

Next to that, mpMRI information is also incorporated in our prediction tool. mpMRI-based T-staging was selected as strong predictor variable for LNI. This result is in accordance with the findings of Gandaglia et al. who also investigated the benefit of including mpMRI and MRI-targeted biopsy data in a nomogram to predict LNI²⁹. The main difference between both prediction models is the fact that the diameter of the index lesion on mpMRI was selected as volume estimator by Gandaglia et al, whereas in our model the maximum tumor-involvement-in-one-core is used as a surrogate for tumor volume. Inclusion of tumor location and tumor multifocality, both determined on mpMRI, as covariables into multivariable models predicting LNI did not improve the accuracy of our built prediction model.

As predictive tools that are developed in one population may not be applicable to another patient population, external validation of our add-on prediction tool was performed using another patient cohort, diagnosed and treated in another hospital. This showed an AUC of 0.73, which is in the order

of magnitude of the external validation by Grivas et al. of the Winter (AUC=0.75), Briganti (AUC=0.75) and MSKCC (AUC=0.74) nomogram³⁰.

From a clinical perspective, our model is of additional value next to the MSKCC and updated Briganti DRE-based nomograms⁸⁻¹⁰ in case of anteriorly located prostate tumors which are difficult to evaluate by DRE. Furthermore, as the tumor volume is estimated by the overall maximum tumor-length-involvement-in-one-core instead of the percentage of positive cores⁸⁻¹⁰, our tool can cope with different biopsy strategies and is congruent with the paradigm shift from systematic biopsies towards targeted biopsies.

The limitations of this study relate to the retrospective review of the collected data. While in our cohort all high risk and high-intermediate risk PCa patients undergo ePLND, low-intermediate risk patients were selected for ePLND based on the existing nomograms. However, in particular in this cohort our prediction tool could be of added value as this is based on state-of-the-art available clinical information. Furthermore, bias associated with a surgical series from a single centre could not be avoided. However, we tried to cope with this limitation by performing an external validation of our developed model. Another study limitation is the fact that mpMRIs were read by different urologists as part of the clinical routine, leading to potential differences in the interpretation of mpMRIs. Nevertheless, the radiology workflow is representative of the majority of clinical practices in the Western world and the PI-RADS v2 scoring system helps to overcome this problem of inter-observer variability²⁰. Furthermore, biopsy ISUP grading and identification of LNI might vary according to the experience of the pathologist. For model building, only patients were selected for whom the histopathologic work-up was performed by high-volume urologists.

Conclusions

A novel, contemporary add-on prediction tool to the existing DRE-based nomograms for men undergoing mpMRI staging and targeted or systematic biopsies should be used to identify patients at high risk of LNI who should be considered for ePLND. Vice versa, by using this add-on tool, unnecessary ePLNDs in patients without LNI could be avoided.

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Legends to the tables

Table 1: Pre- and postoperative descriptive statistics of 420 patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy and pelvic lymph node dissection (≥ 10 lymph nodes (LNs) removed) between 2008 and 2018

Table 2: Comparison and selection of best predicting biopsy information combination for lymph node invasion (LNI)

Table 3: Multivariable logistic regression analyses predicting the presence of LNI in 420 patients

Table 4: Pre- and postoperative descriptive statistics of 187 patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy and pelvic lymph node dissection (≥ 10 lymph nodes (LNs) removed) at AZ Groeninge hospital between 2015 and 2018 (external validation)

Table 5: Systematic analysis of cut-offs used to discriminate between patients with or without pathological lymph node invasion (LNI)

Legends to illustrations

Figure 1: QR-code for an online nomogram application predicting the probability of lymph node invasion (LNI) in patients undergoing an extended pelvic lymph node dissection (ePLND) based on our ISUP- and PI-RADS-based model. The prediction is estimated by:

predicted probability LNI = $\frac{e^{\mu}}{1 + e^{\mu}}$; μ = summation of the intercept term and every model parameter's coefficient (Table 3) multiplied by the corresponding parameter value for the individual patient.

Figure 2: Calibration plot for the mpMRI and ISUP based nomogram. The entire external validation cohort was classified in deciles according to their predicted risk for LNI. A dot was drawn for each decile showing the observed versus expected risk for LNI. The expected risk is the average of the predicted risk per decile.

Figure 3: Decision curve analysis demonstrating the net benefit associated with use of the novel nomogram for detection of lymph node invasion. The x-axis is the threshold to perform an ePLND, that is the probability of LNI at which a man would elect an ePLND. The y-axis represents the clinical net benefit in terms of the probability of positive results (i.e. performing an ePLND in case of LNI) , minus the probability of false-positive results (i.e. performing an unnecessary ePLND without LNI), with the latter weighted by the odds at the threshold.

1

2 Abbreviations

3

4	PCa	Prostate Cancer
5	ePLND	Extended pelvic lymph node dissection
6	LNI	Lymph node invasion
7	PSA	Prostate specific antigen
8	ADT	Androgen deprivation therapy
9	cT-stage	Clinical tumor stage
10	EAU	European Association of Urology
11	NCCN	National Comprehensive Cancer Network
12	mpMRI	Multiparametric MRI
13	DRE	Digital Rectal Examination
14	iT-stage	Image-based tumor stage
15	UZL	University Hospitals Leuven
16	AZG	AZ Groeninge Hospital Kortrijk
17	RP	Radical prostatectomy
18	iPSA	Initial PSA
19	ISUP	International Society of Urological Pathology
20	AIC	Akaike's information criterion
21	C-index	Concordance index
22	AUC	Area under the receiver operating characteristic curve
23	IQR	Interquartile range

Table 1 – Pre- and postoperative descriptive statistics of 420 patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy and pelvic lymph node dissection (≥ 10 lymph nodes (LNs) removed) between 2008 and 2018

	Overall (n = 420)	pN0 (n = 349, 83.1 %)	pN1 (n = 71, 16.9 %)	p value
Age at surgery (year)				
Median (IQR)	65 (60 – 70)	65 (60 – 70)	67 (59 – 70)	0.763
Preoperative PSA (ng/mL)				
Median (IQR)	8.3 (5.9 – 12.5)	7.8 (5.8 – 11.5)	10.4 (7.1 – 14.7)	0.004
Tumor-stage on mpMRI (%)				
iT1c	15 (3.6)	15 (4.3)	0 (0.0)	< 0.001
iT2a-2b	120 (28.6)	113 (32.4)	7 (9.9)	
iT2c	45 (10.7)	41 (11.7)	4 (5.6)	
iT3a	182 (43.3)	147 (42.1)	35 (49.3)	
iT3b	42 (10.0)	20 (5.7)	22 (31.0)	
iT4	16 (3.8)	13 (3.7)	3 (4.2)	
Multifocality on mpMRI (%)*				
No	278 (66.2)	225 (64.5)	53 (74.6)	0.098
Yes	142 (33.8)	124 (35.5)	18 (25.4)	
Tumor location on mpMRI (%)				
iT1c	15 (3.6)	15 (4.3)	0 (0.0)	< 0.001
Peripheral zone	247 (58.8)	188 (53.9)	59 (83.1)	
Transition zone	88 (21.0)	84 (24.1)	4 (5.6)	
Peripheral & transition zone	70 (16.7)	62 (17.8)	8 (11.3)	
Maximum tumor length of single core involvement of highest ISUP grade PCa (mm)				
Median (IQR)	7.0 (4.0 – 10.0)	7.0 (4.0 – 10.0)	10.0 (7.0 – 12.0)	< 0.001
Maximum percentage of single core involvement of highest ISUP grade PCa				
Median (IQR)	65.5 (33.0 – 86.0)	60.0 (30.0 – 81.0)	83.0 (63.0 – 93.0)	< 0.001
Biopsy highest ISUP grade group (%)				
1	18 (4.3)	18 (5.6)	0 (0.0)	< 0.001
2	158 (37.6)	142 (40.7)	16 (22.5)	
3	111 (26.4)	95 (27.2)	16 (22.5)	
4	68 (16.2)	53 (15.2)	15 (21.1)	
5	65 (15.5)	41 (11.7)	24 (33.8)	
Maximum tumor length of single core involvement (mm)				
Median (IQR)	8.0 (5.5 – 11.0)	8.0 (5.0 – 10.0)	11.0 (9.0 – 13.0)	< 0.001
Maximum percentage of single core involvement (%)				
Median (IQR)	71.0 (50.0 – 90.0)	67.0 (46.0 – 85.0)	86.0 (70.0 – 94.5)	< 0.001
ISUP grade group corresponding to maximum tumor length (%)				
1	40 (9.5)	39 (11.2)	1 (1.4)	< 0.001
2	177 (42.14)	156 (44.7)	21 (29.6)	
3	95 (22.6)	81 (23.2)	14 (19.7)	
4	57 (13.6)	44 (12.6)	13 (18.3)	
5	51 (12.1)	29 (8.3)	22 (31.0)	
Percentage of positive cores				
Median (IQR)	50.0 (33.0 – 73.0)	50.0 (30.0 – 66.7)	63.6 (50.0 – 95.0)	< 0.001
Percentage of positive cores with highest ISUP grade PCa				
Median (IQR)	25.0 (14.0 – 50.0)	25.0 (14.3 – 50.0)	33.3 (16.7 – 59.2)	0.094

Percentage of positive cores with lower ISUP grade PCa				
Median (IQR)	10.0 (0.0 – 31.0)	9.1 (0.0 – 30.0)	18.2 (0.0 – 40.8)	0.051
Percentage of positive cores with most common ISUP grade PCa				
Median (IQR)	33.0 (20.0 – 58.0)	33.3 (20.0 – 57.1)	45.5 (29.3 – 63.3)	0.005
Most common ISUP grade group based on percentage of positive cores (%)				
1	53 (12.6)	52 (14.9)	1 (1.4)	< 0.001
2	191 (45.5)	165 (47.3)	26 (36.6)	
3	80 (19.1)	66 (18.9)	14 (19.7)	
4	52 (12.4)	40 (11.5)	12 (16.9)	
5	44 (10.5)	26 (7.4)	18 (25.4)	
Pathological stage (%)				
pT2	207 (49.3)	198 (56.7)	9 (12.7)	< 0.001
pT3a	135 (32.1)	114 (32.7)	21 (29.6)	
pT3b	70 (16.7)	32 (9.2)	38 (53.5)	
pT4	8 (1.9)	5 (1.4)	3 (4.2)	
Positive surgical margins (%)	93 (22.1)	61 (17.5)	32 (45.1)	< 0.001
Pathology ISUP grade group (%)				
1	19 (4.5)	19 (5.4)	0 (0.0)	< 0.001
2	189 (45.0)	178 (51.0)	11 (15.5)	
3	116 (27.6)	91 (26.1)	25 (35.2)	
4	48 (11.4)	35 (10.0)	13 (18.3)	
5	48 (11.4)	26 (7.4)	22 (31.0)	
Tumor volume (mL)				
Median (IQR)	3.3 (1.7 – 6.3)	3.0 (1.7 – 5.5)	5.8 (3.5 – 9.5)	< 0.001
Number of removed lymph nodes				
Median (IQR)	21 (16 – 27)	20 (15 – 27)	25 (20 – 30)	< 0.001
Number of positive lymph nodes				
Median (IQR)	0 (0 – 0)	0 (0 – 0)	2 (1 – 3)	< 0.001
IQR = interquartile range; PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging; ISUP = International Society of Urological Pathology				
* Multifocal prostate cancer was defined as the visualization of at least two tumoral localizations in the prostate on mpMRI.				

Table 2 – Comparison and selection of best predicting biopsy information combination for lymph node invasion (LNI)

	C-index (95 % CI)	AIC
Model 1		
Highest ISUP grade group (1a)	0.68 (0.61; 0.75)	358.89
Maximum tumor length corresponding to 1a (mm) (1b)	0.71 (0.64; 0.77)	354.71
Maximum tumor involvement corresponding to 1a (%) (1c)	0.69 (0.62; 0.75)	359.41
1a + 1b (additional effect)	0.77 (0.71; 0.83)	332.63
1a * 1b (interaction effect)	0.77 (0.71; 0.82)	334.11
Model 2		
Maximum tumor-length-in-one-core (mm) (2a)	0.72 (0.66; 0.78)	352.33
Maximum tumor-involvement-in-one-core (%) (2b)	0.69 (0.63; 0.75)	356.69
ISUP grade group corresponding to 2a (2c)	0.69 (0.62; 0.75)	355.29
2a + 2c (additional effect)	0.78 (0.73; 0.84)	327.35
2a * 2c (interaction effect)	0.78 (0.73; 0.84)	328.87
Model 3		
Percentage of positive cores (3a)	0.64 (0.58; 0.71)	372.16
Percentage of cores with highest grade PCa + percentage of cores with lower grade PCa (3b)	0.64 (0.58; 0.71)	372.71
Model 4		
Percentage of cores with most common ISUP grade group (4a)	0.60 (0.54; 0.67)	379.57
ISUP grade group corresponding to 4a (4b)	0.67 (0.61; 0.67)	360.20
4a + 4b (additional effect)	0.71 (0.65; 0.77)	357.08
4a * 4c (interaction effect)	0.71 (0.64; 0.77)	358.34
CI = confidence interval; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging		

Table 3 – Multivariable logistic regression analyses predicting the presence of LNI in 420 patients

	Odds Ratio (95 % CI)	<i>p</i> value	Parameter estimate
Intercept	-	-	-6.4605
mpMRI-based T stage	1.467 (1.163; 1.850)	0.0012	0.3833
iPSA	1.023 (1.000; 1.046)	0.0457	0.0228
Maximum tumor-length-in-one-core (mm)	1.155 (1.061; 1.258)	0.0009	0.1443
ISUP grade group corresponding to maximum tumor length	1.863 (1.466; 2.367)	< 0.0001	0.6220
CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; iPSA = initial prostate specific antigen; ISUP = International Society of Urological Pathology			

Table 4 – Pre- and postoperative descriptive statistics of 187 patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy and pelvic lymph node dissection (≥ 10 lymph nodes (LNs) removed) at AZ Groeninge hospital between 2015 and 2018 (external validation)

	External validation cohort (n = 187)					
Age at surgery (year);	66					
Median (IQR)	(60-72)					
Preoperative PSA;	8.4					
Median (IQR)	(6.4-11.7)					
Tumor-stage on mpMRI (%)	iT1c:	iT2a-2b	iT2c	iT3a	iT3b	iT4
	2 (1.1)	41 (21.9)	61 (24.1)	71 (38.0)	12 (6.4)	0 (0.0)
Maximum tumor length of single core involvement (mm)	10.5 (8.4-12.9)					
ISUP grade group corresponding to maximum tumor length (%)	ISUP 1:	ISUP 2:	ISUP 3:	ISUP 4:	ISUP 5:	
	17 (9.1)	103 (55.1)	34 (18.2)	22 (11.8)	11 (5.8)	
Pathological tumor-stage (%)	pT2	pT3a	pT3b	pT4		
	116 (62.0)	37 (19.8)	33 (17.6)	1 (0.5)		
Pathology ISUP grade group (%)	ISUP 1:	ISUP 2:	ISUP 3:	ISUP 4:		
	16 (8.5)	101 (54.0)	45 (24.1)	13 (7.0)		
Number of removed lymph nodes;	16					
Median (IQR)	(13-19)					
IQR = interquartile range; PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging; ISUP = International Society of Urological Pathology						

Table 5 – Systematic analysis of cut-offs used to discriminate between patients with or without pathological lymph node invasion (LNI)

CUT-OFF CALCULATED PROBABILITY OF LNI, %	PATIENTS IN WHOM EPLND IS NOT (%) / IS (%) RECOMMENDED	PATIENTS BELOW CUT-OFF WITHOUT (%) / WITH (%) LNI	PATIENTS ABOVE CUT-OFF WITHOUT (%) / WITH (%) LNI	EPLND SPARED, %	LNI MISSED, %
0	0 (0.0) / 420 (100)	0 (0.0) / 0 (0.0)	349 (83.0) / 71 (16.9)	0.0	0.0
1	6 (1.4) / 414 (98.6)	6 (100) / 0 (0.0)	343 (82.9) / 71 (17.1)	1.7	0.0
2	26 (6.2) / 394 (93.8)	26 (100) / 0 (0.0)	323 (82.0) / 71 (18.0)	7.4	0.0
3	49 (11.7) / 371 (88.3)	49 (100) / 0 (0.0)	300 (80.9) / 71 (19.1)	14.0	0.0
4	67 (16.0) / 353 (84.0)	67 (100) / 0 (0.0)	282 (79.9) / 71 (20.1)	19.2	0.0
5	91 (21.7) / 329 (78.3)	91 (100) / 0 (0.0)	258 (78.4) / 71 (21.6)	26.1	0.0
6	107 (25.5) / 313 (74.5)	106 (99.1) / 1 (0.9)	243 (77.6) / 70 (22.4)	30.7	1.4
7	116 (27.6) / 304 (72.4)	114 (98.3) / 2 (1.7)	235 (77.3) / 69 (22.7)	33.2	2.8
8	127 (30.2) / 293 (69.8)	125 (98.4) / 2 (1.6)	224 (76.5) / 69 (23.5)	36.4	2.8
9	138 (32.9) / 282 (67.1)	134 (97.1) / 4 (2.9)	215 (76.2) / 67 (23.8)	39.5	5.6
10	156 (37.1) / 264 (62.9)	150 (96.2) / 6 (3.8)	199 (75.4) / 65 (24.6)	44.7	8.5
11	169 (40.2) / 251 (59.8)	162 (95.9) / 7 (4.1)	187 (74.5) / 64 (25.5)	48.4	9.9
12	180 (42.9) / 240 (57.1)	172 (95.6) / 8 (4.4)	177 (73.8) / 63 (26.3)	51.6	11.3
13	191 (45.5) / 229 (54.5)	182 (95.3) / 9 (4.7)	167 (72.9) / 62 (27.1)	54.7	12.7
14	206 (49.0) / 214 (51.0)	196 (95.1) / 10 (4.9)	153 (71.5) / 61 (28.5)	59.0	14.0
15	218 (51.9) / 202 (48.1)	205 (94.0) / 13 (6.0)	144 (71.3) / 58 (28.7)	62.5	18.3
16	228 (54.3) / 192 (45.7)	213 (93.4) / 15 (6.6)	136 (70.8) / 56 (29.2)	65.3	21.1
17	239 (56.9) / 181 (43.1)	221 (92.5) / 18 (7.5)	128 (70.7) / 53 (29.3)	68.5	25.4
18	246 (58.6) / 174 (41.4)	227 (92.3) / 19 (7.7)	122 (70.1) / 52 (29.9)	70.5	26.9
19	257 (61.2) / 163 (38.8)	237 (92.2) / 20 (7.8)	112 (68.7) / 51 (31.3)	73.6	28.2
20	262 (62.4) / 158 (37.6)	242 (92.4) / 20 (7.6)	107 (67.7) / 51 (32.3)	75.1	28.2

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